Electronic Supplementary Material (ESI) for Integrative Biology.

Supplement S1

Module I

The following equations were implemented and solved in Matlab (R2016a, The MathWorks, Inc., Natick, Massachusetts, United States):

$$\frac{dc(1)}{dt} = \frac{P * A_{gut} * \left(c(2) - c(1)\right)}{V_{gut,ap}} \tag{1}$$

$$\frac{dc(2)}{dt} = \frac{P * A_{gut} * \left(c(1) - c(2)\right) + Q_{gut} * (c(4) - c(2))}{V_{gut,bas}} \tag{2}$$

$$\frac{dc(3)}{dt} = \frac{Q_{gut} * c(2) + Q_{liv} * c(4) - (Q_{liv} + Q_{gut} + Cl_l) * c(3)}{V_{liv}} \tag{3}$$

$$\frac{dc(4)}{dt} = \frac{(Q_{liv} + Q_{gut}) * (c(3) - c(4))}{V_{mix}} \tag{4}$$

where c(i) is the concentration at time t for every compartment, P is the permeability coefficient between the apical and basolateral site of the gut, A_{gut} is the surface area between the gut compartments, Q_i refers to the flow and V_i to the volumes of each compartment.

Module II

The following equations were implemented and solved in Matlab (R2016a, The MathWorks, Inc., Natick, Massachusetts, United States):

$$\frac{dc(1)}{dt} = \frac{P * A_{gut} * \left(c(2) - c(1)\right)}{V_{gut,ap}} \tag{1}$$

$$\frac{dc(2)}{dt} = \frac{V_{gut,bas}}{V_{gut,bas} + dil/comp} * \frac{P * A_{gut} * \left(c(1) - c(2)\right) + Q_{gut} * (c(4) - c(2))}{V_{gut,bas}} \tag{2}$$

$$\frac{dc(3)}{dt} = \frac{V_{liv}}{V_{liv} + dil/comp} * \frac{Q_{gut} * c(2) + Q_{liv} * c(4) - (Q_{liv} + Q_{gut} + Cl_l) * c(3)}{V_{liv}} \tag{3}$$

$$\frac{dc(4)}{dt} = \frac{V_{mix}}{V_{mix} + dil/comp} * \frac{\left(Q_{liv} + Q_{gut}\right) * c(3) + (Q_{kid} - Q_{kid,ap}) * c(5) - (Q_{gut} + Q_{liv} + Q_{kid}) * c(4)}{V_{mix}} \quad (4)$$

$$\frac{dc(5)}{dt} = \frac{V_{kid,bas}}{V_{kid,bas} + dil/comp} * \frac{Q_{kid,bas} * \left(c(4) - c(5)\right) + P_{kid} * A_{kid} * \left(c(6) - c(5)\right)}{V_{kid,bas}} \quad (5)$$

$$\frac{dc(6)}{dt} = \frac{V_{k,ap}}{V_{k,ap} + dil/comp} * \frac{Q_{kid,ap} * c(4) + P_{kid} * A_{kid} * (c(5) - c(6)) - Q_{waste} * c(6))}{V_{k,ap}} \quad (6)$$

$$\frac{dc(7)}{dt} = \frac{V_{waste}}{V_{waste} + dil/comp} * \frac{Q_{waste} * c(6)}{Q_{waste} * t} \quad (7)$$

where dil/comp is a time-dependent value to account for dilution effects due to media replenishment and loss of drug via excretion to the waste container.

Supplemental Figures

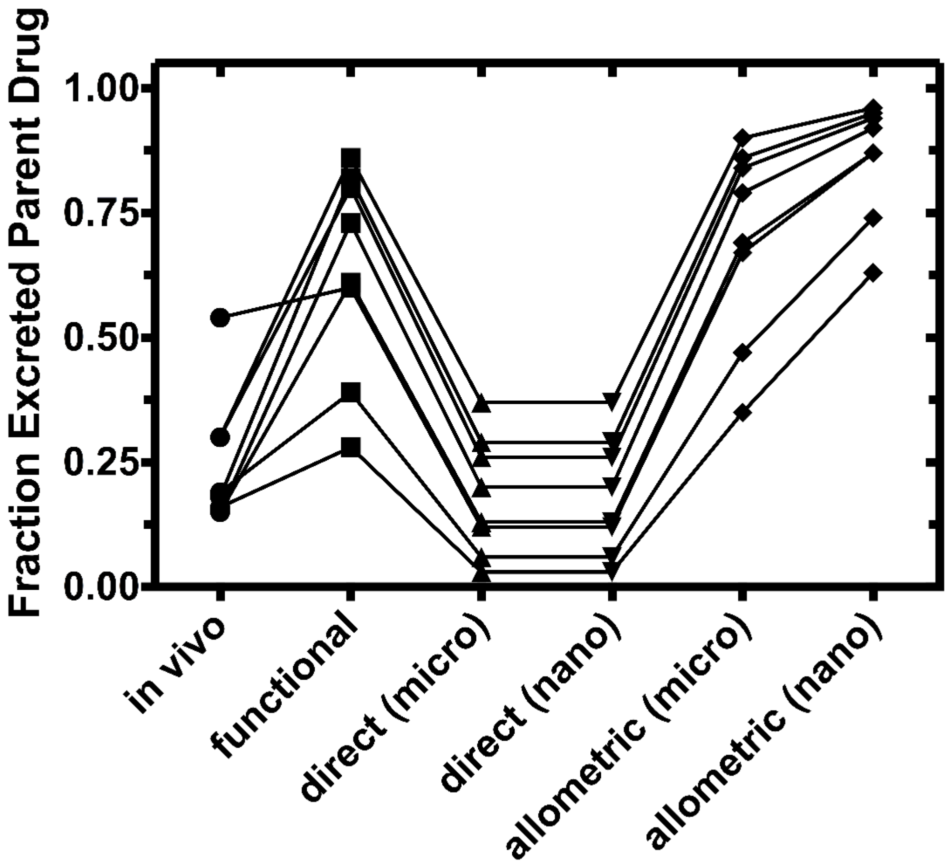
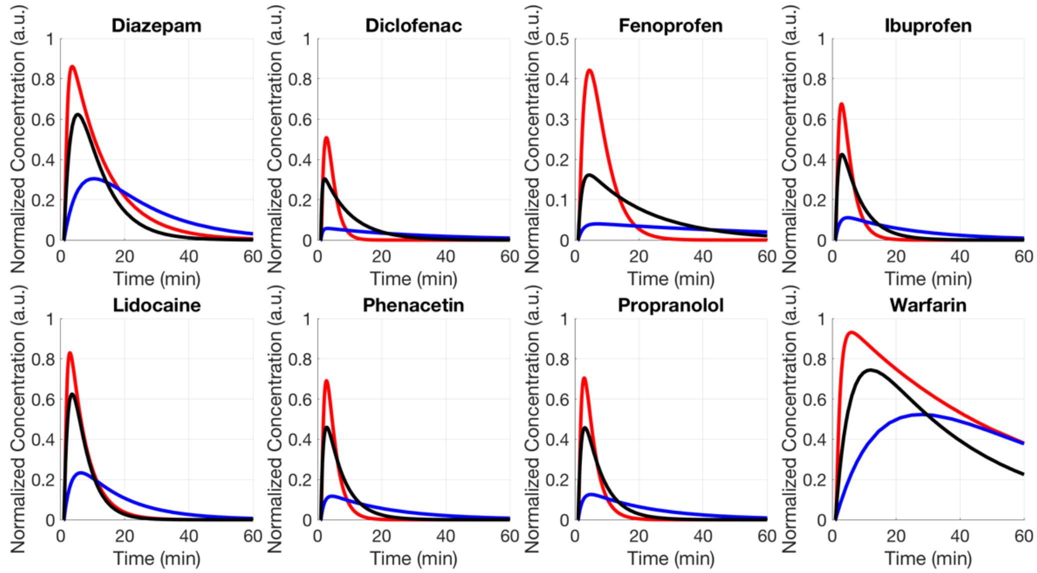


Fig. S1.: Estimated fraction excreted parent drug in module II for clinically reported values and all scaling approaches. The multi-functional scaling approach yields values close to *in vivo*. Direct and allometric scaling resulted in platform designs that systematically under- and overpredicted the excreted fraction of unchanged parent drug in the multi-MPS platform, respectively.

(a)



(b)

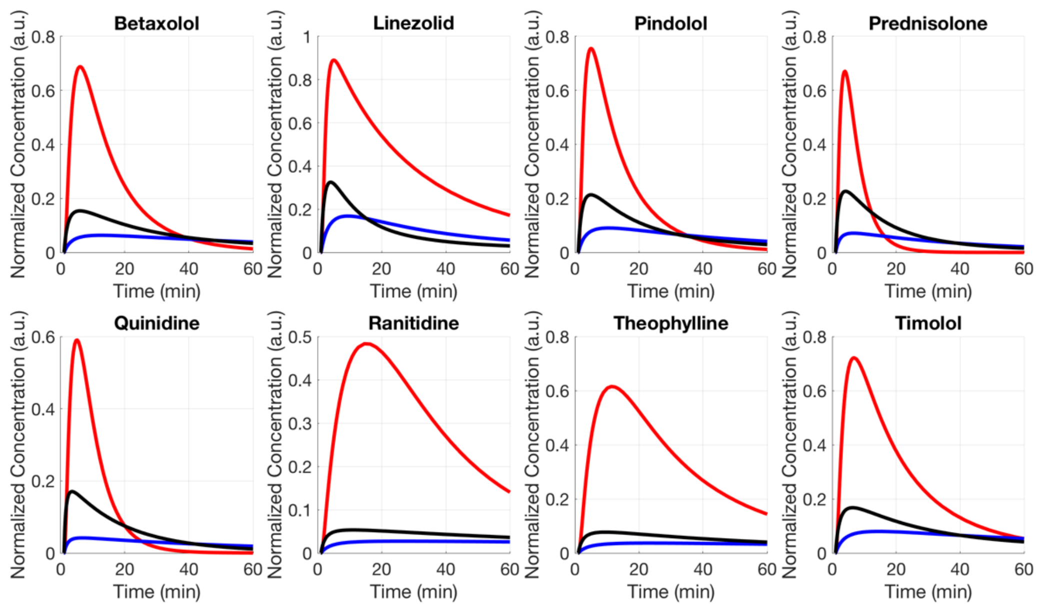


Fig. S2.: Simulated drug distribution for (a) module I and (b) module II using direct scaling (micro-human, red) or allometric scaling (micro-human, blue; nano-human, black) to inform the design parameters. Overall, all approaches show (a) fast metabolism and (b) fast metabolism and excretion from the system within minutes. Only direct scaling for both modules was able to yield similar initial peak concentrations.